PANDEMIC INFLUENZA AND THE SWINE INFLUENZA VIRUS[1]

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Evidence points to a repeating, cyclic pattern in the appearance of antigenic shifts in the influenza A virus. Development of the swine influenza strain isolated at Fort Dix, New Jersey, similar to the one that sparked the 1918 pandemic, had been predicted three years earlier.

Influenza Virus

Influenza virus was first isolated from swine in 1930 (*1*) and from man in 1933 (*2*). The virus consists of a nucleoprotein core composed of single-stranded RNA with a segmented genome coding for seven recognized viral proteins (*3*). The nucleoprotein is encapsulated by a double membrane containing a virus-coded inner protein layer and an outer lipid layer of host cell origin. Two proteins, the hemagglutinin (HA) and the neuraminidase (NA), project from the virus surface. Influenza viruses isolated from man have contained four distinct hemagglutinins and two distinct neuraminidases. At least 11 additional types of hemagglutinins and seven additional neuraminidases have been found in viruses isolated from avian, equine, and other animal hosts (*4*).

Nomenclature for the influenza virus is standardized (*4*). Each virus is identified by a distinct signature consisting of: (1) the type of nucleoprotein core (A, B, or C); (2) the animal host from which the virus was isolated; (3) the location of the laboratory in which the isolation was made; (4) the laboratory number for that particular isolate; and (5) the year in which the isolation was made. The designation for influenza A viruses also includes (6) the type of hemagglutin and (7) the type of neuraminidase present. For example, an influenza virus isolated from a swine in Michigan in 1965 is designated A/swine/Michigan/2/65(HswlN1). For viruses isolated from man, the host designation is not included in the name. For example, A/Victoria/3/75(H3N2) refers to the strain which caused the 1975-1976 epidemic. The virus responsible for the recent "swine-type influenza" in man is identified as A/New Jersey/8/76(HswlN1).

One of the unique characteristics of the influenza virus is that the hemagglutinin and the neuraminidase undergo frequent antigenic changes. Minor changes, which occur relatively often, are referred to as

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antigenic drifts. Antigenic drift is thought to result from the selection of mutants through increasing antibody pressure in the human population. At longer intervals, major changes, referred to as *antigenic shifts*, take place in the hemagglutinin or neuraminidase. The origin of these shifts remains uncertain: they might be caused by the direct transmission of antigenic variants from reservoirs in human or nonhuman hosts; they could be the result of genetic recombination of human and animal strains of influenza; or they might simply be the end product of a series of mutations (*5, 6*).

Epidemiology of Influenza

The occurrence of influenza epidemics depends upon a poorly understood interaction of virus, population susceptibility, and environmental conditions. When conditions are suitable, epidemics may occur rapidly, affecting large numbers of people and causing many deaths.

Both the influenza A and B viruses have been associated with major epidemics in human populations, but only influenza A has been consistently associated with pandemics. Pandemics are major epidemics due to a single virus type which sweep around the world in a short period of time and cause marked increases in mortality. They are associated with major antigenic shifts. Human populations with no previous exposure to newly appearing antigens have no immunity and hence no protection against the new strain.

Following an antigenic shift and the associated pandemic, a period of interpandemic influenza ensues. During these years a series of smaller epidemics takes place due to viruses which are related to the previous pandemic strain but which have slight differences in the surface antigens (antigenic drifts). Morbidity and mortality associated with these epidemics are much lower than in the preceding pandemic.

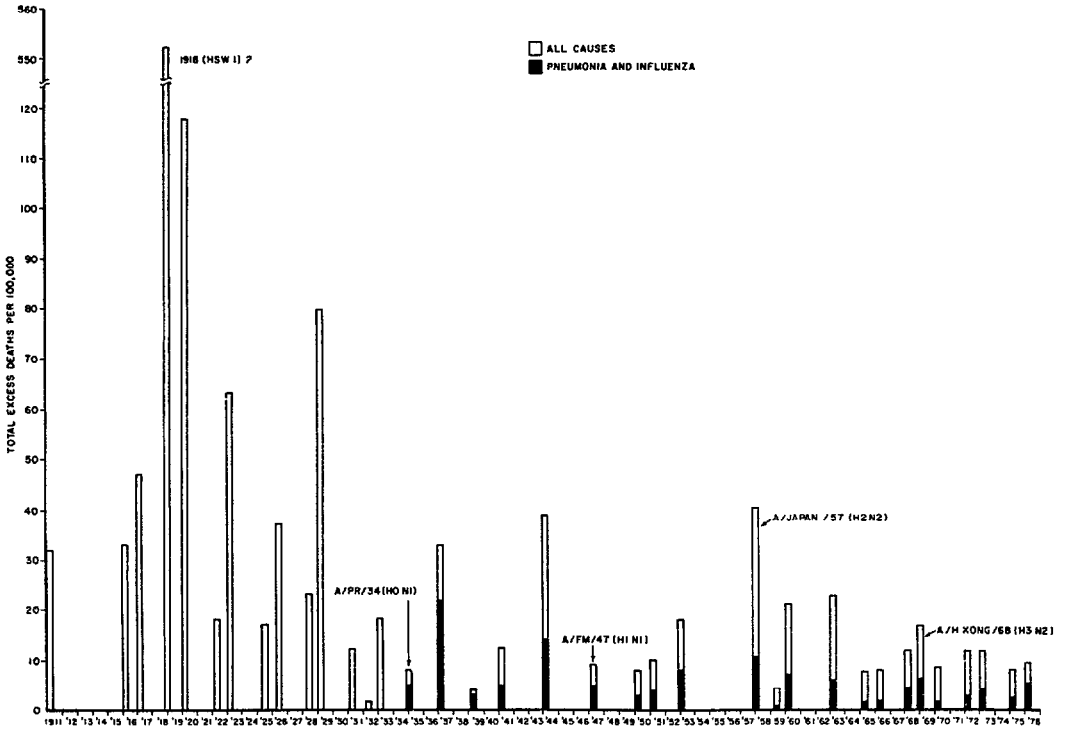
The rapidity with which pandemic influenza can spread is a phenomenon unique in the history of infectious diseases. In the well-studied pandemics of 1957 and 1968 the time lapse from the initial reporting of isolation of a new strain of influenza to the dissemination of disease to all major areas in the world was under six months. The first outbreak of disease in 1957 was reported in China in late February (*7, 8*). By early June cases of illness due to this new strain, subsequently called "Asian flu," had already begun to occur in the United States of America, and by the end of October outbreaks were being reported from all parts of the country. A similar pattern was seen 11 years later with the Hong Kong strain: it was first isolated from cases in Asia on 17 July 1968 (*9*), outbreaks in the United States began in September, and by December the disease had extended to the entire country (*10*).

The reasons for the rapid spread of influenza are only partly understood. Doubtlessly important are: the short incubation period (24-48 hours), the large size of the population susceptible to infection, and the virus' easy transmissibility. The fact that epidemics occur most often in the winter suggests that cold weather may also play a role. Since it has been observed that widespread simultaneous outbreaks develop following a period of sporadic cases, it has been postulated that virus is seeded in the susceptible population by mildly ill individuals.

Morbidity and Mortality

Influenza epidemics characteristically cause widespread illness, attacking as much as 20 or 30 per cent of the population. The case-fatality rate is in fact quite low—less than 1 per cent—but because there are so many cases the actual number of deaths is large. Individual cases of clinical influenza may be mild, especially in otherwise healthy individuals, but still the large numbers of

Figure 1. **Excess mortality during epidemic periods, United States of America, 1911-1976.**



Source: Data from United States Public Health Service, Center for Disease Control, Bureau of Epidemiology.

patients place a heavy burden on available medical and emergency-room services. Moreover, the illness-associated absenteeism has a nationwide effect. Finally, complications, such as bacterial superinfections, often result in hospitalization.

The impact of influenza pandemics has been measured since the early 1800's by the number of deaths occurring during the epidemic in excess of the number normally expected from all causes during the period in question (Figure 1). Especially evident are excess deaths in the cause category "pneumonia and influenza." In the United States the excess deaths in this category are almost always due to influenza. Mortality is usually highest among the elderly and in persons with such chronic conditions as pulmonary or cardiovascular disease. During the pandemics—as in 1918, 1957, and 1968—mortality has been most marked at the beginning. Excess mortality has also been observed in interpandemic years (Table 1).

The worst influenza pandemic on record occurred in 1918. It caused approximately half a million deaths in the United States of America and an estimated 20 million deaths worldwide (*11*). Estimated death rates in the United States ranged between 400 and 598 per 100,000 population (*11, 12, 13*), and rates as high as 6,000 per 100,000 were reported from some countries and in concentrations of military personnel (*11, 14*). An unusual feature of this pandemic was that excess mortality was most marked in persons aged 20 to 40. The recent experiences have more specific data to offer.

Table 1. Excess mortality due to pneumonia and influenza, 1957-1976.

Period of excess mortality[a]	Population (1,000's)	Estimated number of excess deaths due to pneumonia and influenza	Rate of excess P and I deaths per 100,000	Estimated total excess deaths	Rate of total excess deaths per 100,000 population	Type of influenza
Oct 1957-Mar 1958	173,232	18,500	10.7	69,800	40.3	A/(H2N2)
Mar-Apr 1959	176,420	1,400	0.8	7,900	4.5	A/(H2N2)
Jan-Mar 1960	179,323	12,700	7.1	38,000	21.2	A/(H2N2)
Jan-Mar 1962	185,890	3,500	1.9	17,100	9.2	B
Feb-Mar 1963	188,658	11,500	6.1	43,200	22.9	A/(H2N2)
Feb-Mar 1965	193,818	2,900	1.5	14,900	7.7	A/(H2N2)
Feb-Apr 1966	195,875	3,700	1.9	15,900	8.1	A/(H2N2)
Jan-Feb 1968	199,846	9,000	4.5	23,800	11.9	A/(H2N2)
Dec 1968-Jan 1969	201,921	12,700	6.3	33,800	16.7	A/(H3N2)
Jan-Feb 1970	203,736	3,500	1.7	17,200	8.5	A/(H3N2)
Jan-Feb 1972	208,232	5,600	2.7	24,600	11.8	A/(H3N2)
Jan-Feb 1973[b]	209,851	6,700	3.2	24,800	11.8	A/(H3N2)
Jan-Feb 1975[c]	211,390	5,300	2.5	17,400	8.2	A/(H3N2)
Feb-Apr 1976[c]	213,000	11,400	5.4	20,000	9.4	A/(H3N2)

[a]No excess mortality observed in 1961, 1964, 1967, 1971, or 1974.

[b]Based on a 10% sample of mortality data from the National Center for Health Statistics. The mortality data for the earlier periods are based on final NCHS data.

[c]Estimates based on extrapolation of mortality data collected by CDC from 121 U.S. cities.

In the United States during the winter of 1957-1958 there were some 69,800 excess deaths, and in 1968 the figure calculated was 33,800 excess deaths.

Virologic Characterization

The understanding of influenza virology and epidemiology has increased as laboratory techniques have improved. Precise virologic characterization of the influenza A viruses according to type of surface antigen can be made only for those viruses that have been present since the 1930's, when viral isolation first became possible. However, from serologic studies of individuals born since the mid-1800's, inferences have been made about the antigenic character of earlier strains of virus. These studies have been possible because persons infected with an influenza virus maintain antibody throughout life against the surface antigens of the strains by which they were first infected, an immunologic phenomenon referred to as the "doctrine of original antigenic sin" (*16*).

Evidence now suggests that antigens which were prevalent at one time may again become prevalent when population immunity wanes. Some investigators have interpreted serologic data to indicate that viruses related to the 1957-1958 Asian strains (H2) were prevalent in the late nineteenth century (*17*). These strains were apparently followed in turn (*18, 19, 20*) by ones whose hemagglutinin type (H3) was similar to that of A/Hong Kong/1/68 (H3N2), although the neuraminidase was quite distinct (*21*), being more similar to that of the equine Neq2. Similar serologic studies indicate that the 1918 pandemic was due to an HswlN1 virus which had been isolated only from swine until its first isolation from man two years ago (*22*).

As shown in Table 2, four major strains of human influenza virus have been isolated since the 1930's: A/Puerto Rico/8/34 (H0N1), A/Fort Monmouth/1/47 (H1N1), A/Japan/305/57 (H2N2), and A/Hong Kong/1/68 (H3N2). Virologic characterization at the time of the 1957-1958 pandemic (Japan strain) indicated that the hemagglutinin and the neuraminidase were totally different from those of the earlier viruses. Smaller epidemics during the next 10 years were caused by viruses related to the H2N2 reference strain. The most recent pandemic occurred in 1968 and was caused by a strain whose reference was designated A/Hong Kong/1/68 (H3N2). In this strain an antigenic shift in the hemagglutinin, but not the neuraminidase, had occurred. Since 1968 there have been six epidemics due to related H3N2 viruses, the most recent being due to strains designated A/Port Chalmers/1/73 (H2N2) and A/Victoria/3/75 (H3N2).

Table 2. History of influenza A in man.

1880-1910?	H2 and H3 hemagglutinins may have circulated sequentially as determined from serologic studies of antibody prevalence in persons who were children during these years.
1918	Pandemic probably due to (HswlN1)-like virus as indicated by later serological studies.
1933	A/Walter Smith/33 (H0N1). First influenza virus isolated from man.
1934	A/Puerto Rico/8/34 (H0N1) isolated.
1946	A/Fort Monmouth/1/47 (H1N1). Not a true antigenic shift from H0N1. Not associated with a pandemic.
1957	A/Japan/305/57 (H2N2). Antigenic shift in both antigens. Caused a major pandemic.
1958-1967	Several epidemics due to (H2N2) viruses associated with antigenic drifts.
1968-1969	A/Hong Kong/1/68 (H3N2). Antigenic shift in hemagglutinins only. Caused a moderate pandemic.
1969-1976	Several epidemics due to (H3N2) viruses associated with antigenic drifts.
Feb 1976	A/New Jersey/8/76 (HswlN1) isolated.

The fact that H2 and H3 have occurred in sequence over the past 20-year period has given rise to the hypothesis that H2, H3, and Hswl may have also circulated sequentially in the late nineteenth and early twentieth century. It has been proposed that a limited number of hemagglutinin antigens exist and that they occur in a recycling pattern (*17, 23, 24*). Indeed, Masurel and Marine predicted in 1973 that a swine-like influenza A virus might recur in man during the latter part of this century (*25*).

Swine Influenza Virus

Swine influenza virus (e.g., A/swine/Tennessee/75 (HswlN1) is distinguished by its surface antigens (*4*). Some antigenic variation among strains is recognized (*26*). Isolation is usually made in eggs. The clinical disease in swine was first recognized in 1918, and the virus was first isolated in 1930 from swine (*1*). The available evidence suggests that the virus spread from man to pigs during the 1918 pandemic (*1*). Extensive studies since 1930 have confirmed that this virus commonly produces disease in swine every year and may be present today in about half of the swine herds in the United States (*27, 28*). The illness in swine consists of fever and upper respiratory symptoms; death in younger pigs and abortions in sows may occur.

Serologic Studies in Man

Although the virus is common in swine, there has been little evidence that it was reentering the human population (*29*). Serologic studies of the general human population show a high prevalence of antibodies to the A/swine virus in persons old enough to have been exposed to influenza prior to the late 1920's (Table 3). The surveys also show increased prevalence of antibodies in younger individuals who have been occupationally exposed to swine. This latter phenomenon may be due to an occasional sporadic human infection with mild symptoms, if any, and no secondary spread. Occupational exposure to the virus may also have resulted in immunization without infection. Interpretation of these serosurvey data must take into account that during the 1950's and early 1960's military personnel were immunized with a vaccine containing swine antigen and that infection or vaccination with H3N2 viruses may produce heterologous antibody responses in some cases (G. R. Noble, personal communication).

Infection in Man

Until recently there was no direct confirmation that A/swine virus antibodies in younger individuals resulted from clinically apparent infections. Since 1974, however, evidence has begun to accumulate that human influenza due to infections with A/swine-like viruses may in fact occur (Table 4). That year a swine-like influenza virus, A/Mayo Clinic/103/74 (HswlN1), was isolated postmortem from the lungs of a 16-year-old boy who died of pneumonia-complicated progressive respiratory insufficiency due to Hodgkin's disease. Prior to his terminal illness, the patient lived on a farm that had pigs which were subsequently shown to have antibody against swine influenza virus (*22*).

In October 1975 a previously healthy 8-year-old boy in rural Wisconsin developed a febrile illness of unknown etiology. Paired sera showed seroconversion to the A/swine virus. This child also lived on a farm where pigs with swine influenza antibodies were present. Investigation of the family showed that of seven household members, five (ages three, four, seven, nine, and 33) had titers against the A/swine virus, suggesting past infection. None had evidence of recent H3N2 infection. None of 24 classmates of the boy had evidence of infection, and the prevalence of A/swine virus antibody among the general commu-

Table 3. Summary results of serologic surveys to determine the prevalence of A/swine influenza antibody in U S. populations.

Year	Location	Population	Age at time blood was drawn				
			No. with titers/No. tested (% of population)				
1966[a]	Illinois	General public	≤15	16-29	30-45	>45	
			1/200(.5)[d]	1/247(.4)	39/242(16)	116/151(77)	
	(Statewide)	Persons occupationally exposed to swine	–	17/182(9.3)	81/413(20)	251/345(72)	
1971[b]	Atlanta, Georgia	Community members	≤16	17-31	32-46	>52	
			1/161(.6)	14/163(8.6)	43/112(38)	217/250(87)	
1976[c]	Atlanta, Georgia	Community members	≤20	21-30	31-40	41-50	>50
			1/37(3)	2/25(8)	9/33(27)	9/25(36)	27/27(100)
1976	Sheboygan, Wisconsin	Community members	≤15	16-29	30-49	>50	
			4/156(3)	2/25(8)	2/19(11)	33/88(87)	
1976	Fayetteville, Pennsylvania	Community members	≤15	16-29	30-49	>50	
			0/60(0)	5/38(13)	9/52(17)	46/52(88)	

[a]Schnurrenberger, et al. (*29*).
[b]Courtesy of Dr. William Marine.
[c]Courtesy of Dr. Gary Noble.
[d]Number having titers/number tested (per cent population).

Table 4. Summary of cases of influenza due to A(HswlN1)-like viruses and of investigations of man-to-man transmission.

Location	Age	Sex	Onset	Diagnostic evidence	Investigation of spread		
					Household contacts	Local contacts	Other parts of community
Mayo Clinic, Rochester, Minnesota	16[a]	M	July-Sept 1974	Virus isolation on postmortem examination	2 breeder sows had antibodies; boy's parents were negative	–	–
Sheboygan, Wisconsin	8[a]	M	Oct 1975	Seroconversion and flu-like illness	5 of 7 household members had Hl titers ≥ 20; none had titers for A/Vic.	0/24 classmates had titers	*Age* ≥ 50 *Post/tested* 33/38 % 87 16-49 4/44 9 ≤15 4/156 3
Fort Dix, New Jersey	19	M	Feb 1976	Virus isolation on postmortem examination	34% positive titers in platoons with confirmed cases	273/1321 (21%) single sera positive	6% positive titers in platoons without confirmed cases
			4 cases	Isolations	–	–	–
			6 cases	Seroconversion	–	–	–
Charlottesville, Virginia	40[a]	F	5 Dec 1975	Pneumonia and seroconversion	0/5 children positive	0/4 cases in close neighbors	–
	55	M	27 Dec 1975	Pneumonia and seroconversion	0/4 cases in household	0/2 positive	4/12 cultures positive for A/Victoria

[a]Had contact with swine prior to illness.

nity was similar to that observed in other serosurveys (*30*).

In January and February 1976, during an outbreak at Fort Dix, New Jersey, of human influenza due to A/Victoria (H3N2), swine influenza-like viruses—including what is now the reference strain, A/New Jersey/8/76 (HswlN1)—were isolated from five recruits, one of whom died of acute viral pneumonia. Six additional cases were confirmed by fourfold rises in titer, and a serologic survey based on single serum specimens indicated that several hundred cases of infection due to A/NJ/8/76-like viruses may have occurred. Thirty-four per cent of 110 close contacts of confirmed cases were found to have A/swine virus antibody, while only 6 per cent of those with no direct contact with known cases had antibody. A comparison of 10 hospitalized cases of A/New Jersey influenza with 10 cases of A/Victoria influenza at Fort Dix during the same period indicated that their illnesses were similar but that A/New Jersey influenza may have been a somewhat milder illness (P. Russell, personal communication). By early March the Fort Dix outbreak was subsiding, and most of the cases that had occurred since early February had been due to A/Victoria (H3N2).

Following the Fort Dix outbreak, the U.S. Center for Disease Control investigated family members and close contacts of 22 recruits who: had entered Fort Dix during the first two weeks in January, reported swine contact prior to entry, and demonstrated antibody against the A/swine virus (*30*). Of 171 civilian contacts of these

Table 5. Investigation of close contacts of 22 recruits at Fort Dix, New Jersey, with history of swine contact and swine antibody.

Community of origin	No. tested	No. with HI ≥ 20 (ages)
Arley, Alabama	4	1 (42)
Headland, Alabama	4	1 (61)
Thornton, Colorado	9	1 (50)
Lyons, Colorado	3	0
Laurel, Delaware	4	0
Kellogg, Iowa	5	0
Franklin, Massachusetts	4	0
Belding, Michigan	13	0
Munnsville, New York	9	0
Everington, Ohio	1	0
Columbus, Ohio	2	0
Valencia, Pennsylvania	4	0
Erie, Pennsylvania	7	0
Fayetteville, Pennsylvania	11	4[a] (11, 12, 20, 25)
Newville, Pennsylvania	4	1 (50)
Hemingway, South Carolina	4	2 (60, 18[b])
Bristol, Tennessee	2	0
Woodstock, Virginia	10	3 (47, 49, 75)
Toppenish, Washington	20	2 (56, 32)
Tacoma, Washington	35	3 (60, 53, 59)
Mannington, West Virginia	11	1 (59)
Wheatland, Wyoming	5	0
Total	171	19

[a] 3 siblings and 1 friend living in same household.
[b] Girlfriend of recruit.

recruits in 22 communities, 19 were found to have antibody titers against A/swine influenza (Table 5). In one family from Fayetteville, Pennsylvania, four individuals (ages 11, 12, 20, and 25) had titers suggesting past infection with A/swine influenza. None had a history of swine contact, suggesting that person-to-person transmission had taken place. Investigation, however, did not indicate that there had been any spread to the community.

Further surveys in 1976 have revealed a number of individuals who have had contact with pigs and have elevated A/swine antibody titers. In addition, two patients with pneumonia and seroconversion against A/swine were found in Charlottesville, Virginia. One of these patients had no history of swine contact and no evidence of A/Victoria infection. Investigation did not indicate spread to immediate contacts or the community (*31*).

SUMMARY

The hemagglutinin and the neuraminidase that project from the surface of the influenza A virus undergo frequent antigenic changes. The minor changes, which occur relatively often, are referred to as antigenic *drifts*. They are associated with small epidemics. The major changes, antigenic *shifts*, involve a total modification in the nature of the hemagglutinin and/or the neuraminidase. Since much of the world's population has no previous immunity against the newly composed virus, the shift brings with it a pandemic that spreads with unique rapidity.

The influenza A viruses isolated from man since the 1930's have contained four distinct hemagglutinins and two distinct neuraminidases. The observation that people maintain high antibody throughout life to the influenza virus that first infects them led to serologic studies of the older population in the United States of America. The results indicated that the hemagglutinin prevalent in 1957-1967, known as H2, and that appearing in 1968, designated H3, may well have circulated in the same sequence over the period 1880-1910. These conclusions gave rise in turn to the hypothesis that a limited number of hemagglutinin antigens exist—perhaps four that are pathogenic for man—and that they occur in a recycling pattern. Thus it was predicted in 1973 that an influenza A virus similar to the one that sparked the tragic 1918 pandemic (Hswl—designated with the "sw" because swine are involved in the transmission cycle) might soon appear.

Isolations of such a virus were in fact made in 1974 and 1975, but in each case the patient had had contact with pigs and careful investigation revealed no further spread in the community. The outbreak at Fort Dix, New Jersey, in 1976 was the first indication since 1918 that man-to-man transmission of Hswl had occurred. A virus containing the Hswl antigen was isolated from five recruits, six additional cases were confirmed by fourfold rises in titer, and a serologic survey indicated that there may have been several hundred such infections.

Influenza has far-reaching importance because of its tremendously high morbidity. Death can ensue, especially when the disease is complicated by pneumonia, and even though the case-fatality rate as such is not high, the great numbers of cases mean that many excess deaths do in fact occur. Moreover, a pandemic causes extensive absenteeism, at cost to the national economy, and places an almost overwhelming burden on medical care, hospital, and other health services.

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